REMARKS

Applicants have amended claims 23 and 27-36 to improve their form. Claims 27, 28, 30, 31, 33, and 34 have been amended to reorder the sets of structure coordinates of IMPDH amino acids which define the binding pocket in these claims. Claim 32 has been amended to an independent claim, incorporating the subject matter of claim 29. Claims 35 and 36 have been amended to recite a molecular complex defined by the structure coordinates of the amino acids of IMPDH and one or more of XMP and MPA. Support for these amendments can be found throughout the specification as originally filed. The above amendments are listed in the enclosed "Appendix of Amendments."

Applicants have added claims 37-62. Support for the addition of claim 37 can be found, for example, on pg. 29, line 7 to pg. 30, line 16 and pg. 32, line 32 to pg. 34, line 17 of the specification as originally filed. Support for the addition of claim 38 can be found, for example, in claims 7 and 23 as originally filed, and on pg. 28, line 20 to pg. 30, line 16 and example 7 of the specification as originally filed. Support for the addition of claim 39 can be found, for example, in examples 2, 3 and 4 of the specification. Support for the addition of claim 40 can be found, for example, on page 19, lines 13-20 and page 29, lines 7-14 of the specification. Support for the addition of claims 41-51 can be found, for example, on pg. 29, line 7 to pg. 34, line 9 in the specification as originally filed. Support for claims 52-62 can be found, for example, on pg. 32, line 32 to pg. 34, line 17 of the specification and claim 23 as originally filed.

None of the amendments adds new matter. Their entry is requested.

The Rejections

35 U.S.C. § 112, first paragraph

In the Examiner's view, claims 23 and 27-36 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification so as to enable one skilled in the art to make and/or use the invention. The Examiner contends that claims 23 and 29 are not enabled since they do not identify in the bodies of the claims the binding pocket coordinates recited in the claims' preambles. The Examiner also alleges that the claims do not recite the structure coordinates of the chemical entity to be used in the fitting operation.

The Examiner contends that the steps of the claims do not have any limitations as to determining the types of associations defined in the specification between the chemical entity and the amino acids of the binding pocket. The Examiner alleges that the metes and bounds of the "fitting operation" are not defined in the specification and that the type of quantification of the results of such an operation is not defined. The Examiner also contends that the specification provides no examples using the structure coordinates of Figure 1 in the method as claimed, that is, no fitting operation is performed for any chemical entity.

The Examiner contends that the claims are not limited to the programs set forth on pages 28-30 and 34 of the specification and that the specification provides no guidance as to other fitting operations and analysis of the results of such fitting operations to quantify an association. The Examiner also alleges that it is unclear from the specification if visual inspection of a three-dimensional structure of a chemical entity in a

docking program with the binding site meets the limitation of quantifying the association. The Examiner contends that although the preamble is directed to evaluating the ability of the chemical entity to associate, there is no evaluation step or cut-off to determine whether or not the chemical entity could be deemed to associate with the binding pocket. The Examiner also alleges that while the specification appears to be directed to novel drug design or known compound identification wherein the structure coordinates of these chemical entities can be positioned in the binding pocket computationally, the claims are not written so as to set forth this concept. Applicants traverse in part and amend in part.

Applicants have amended claims 23 and 29 to recite "said binding pocket" or "the binding pocket" in the body of the claims. Applicants have also amended the claims to recite "structure coordinates of a first chemical entity" in the body of the claims. Applicants have further amended the claims to recite "perform a fitting operation to associate the chemical entity with all or part of said binding pocket" in the steps, thus requiring the fitting operation to achieve an association between the chemical entity and the molecule or molecular complex. Guidance for the performance of a fitting operation to associate the chemical entity with the molecule or molecular complex is found for example, on page 27, line 29 to page 28, line 19, page 29, line 7 to page 30, line 16, page 32, line 32 to page 34, line 17 of the specification. Preferred deformation energies of binding are disclosed, for example, on page 33, lines 7-11 of the specification. The computer programs disclosed in the specification provide guidance for suitable energy cut-off values. Other cut-off values for interactions such as covalent, non-covalent and non-complementary electrostatic interactions are well known to a person skilled in the

art. Applicants direct the Examiner's attention to MPEP 2164.02 wherein it is stated that:

> "The specification need not contain an example if the invention is otherwise disclosed in such [a] manner that one skilled in the art will be able to practice it without an undue amount of experimentation....When considering the factors relating to a determination of non-enablement, if all the other factors point toward enablement, then the absence of working examples will not by itself render the invention non-enabled."

In view of the arguments above, the fitting operation to associate the chemical entity and the molecule or molecular complex is fully enabled employing knowledge and techniques known to the skilled artisan.

Applicants submit that the visual inspection of a three-dimensional structure of a chemical entity in a docking program with the binding site is encompassed by claim 23. Support for this assertion can be found, for example, on pg. 26, lines 26-29 and pg. 29, lines 10-14 of the specification. Applicants have added claim 40 to incorporate this embodiment. In addition, as the specification provides other embodiments of designing new compounds, applicants have added claim 41 and dependent claims to incorporate this embodiment.

In light of the above arguments, applicants submit that the pending claims are fully enabled and request that the Examiner withdraw the rejection under 35 U.S.C. § 112, first paragraph.

35 U.S.C. § 112, second paragraph

In the Examiner's view, claims 28, 31, 34 and 36 are rejected under 35 U.S.C. 112, second paragraph as being indefinite for failing to particularly point out and

distinctly claim the subject matter that the applicant regards as the invention. The Examiner contends that claim 28 is confusing in its dependency on claim 27 since claim 28 defines a binding pocket with fewer coordinates than that which is defined in claim 27 and therefore fails to contain all of the limitations of the claims upon which it depends. The Examiner further alleges that claims 31 and 34 are also confusing in their dependencies on claims 30 and 33, respectively, for the same reason.

Applicants have amended claims 28, 31 and 34 , to depend from claims 23, 29 and 32, respectively, thereby overcoming the rejection.

The Examiner also contends that claim 35 is confusing for failing to further define the binding pocket of claim 29 clearly. In particular, the Examiner alleges that the limitations of this claim refer to the molecule or molecular complex of the preamble which is not required by the body of the claim.

Applicants have amended claim 35 to recite "wherein said molecules is defined by the set of structure coordinates of IMPDH amino acids" and "said molecular complex is defined by the set of structure coordinates of IMPDH amino acids and one or more of XMP and MPA." Claim 35 as amended, defines the molecule or molecular complex separately, thereby overcoming the rejection.

The Examiner also contends that claim 36 is confusing in reciting "wherein said molecule or molecular complex comprises." The Examiner alleges that since three components are listed that only the complex was intended or that any of the recited components may comprise the complex. The Examiner contends that as claim 32

defines the binding pocket, from which claim 36 depends, it is unclear how claim 36 further modifies these coordinates or the claimed method.

Applicants have amended claim 36 to define the molecule or molecular complex separately as follows: "said molecule comprises amino acids 1-514 of IMPDH" and "said molecular complex comprises amino acids 1-514 of IMPDH and one or more of XMP and MPA", thereby overcoming the rejection.

In light of the foregoing arguments, applicants request that the Examiner withdraw the rejection under 35 U.S.C. § 112, second paragraph.

35 U.S.C. § 103(a)

In the Examiner's view, claims 23 and 27-36 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Bohm. The Examiner states that Bohm teaches the computer program LUDI for design of enzyme inhibitors by positioning small molecules into clefts of protein structures, using particular calculations for fragment fitting to interaction sites and outputting the three dimensional representation of the designed molecule in association with the enzyme used as input. Citing MPEP 2106, the Examiner contends that the recited structural coordinates are nonfunctional descriptive material as it functions as input to the computer means.

The Examiner points to the following paragraphs in MPEP 2106 :

> "Common situations involving nonfunctional descriptive material are:
>
> -a computer-readable storage medium that differs from the prior art solely with respect to nonfunctional descriptive material, such as music or a literary work, encoded on the medium,

> -a computer that differs from the prior art solely with respect to nonfunctional descriptive material that cannot alter how the machine functions (i.e., the descriptive material does not reconfigure the computer), or
>
> -a process that differs from the prior art only with respect to nonfunctional descriptive material that cannot alter how the process steps are to be performed to achieve the utility of the invention."

The Examiner contends that how the program Bohm functions is not altered by the input. Citing *In re Gulack*, 703 F.2d 1381 (when descriptive material is not functionally related to the substrate, the descriptive material will not distinguish the invention from the prior art in terms of patentability), the Examiner concludes that the recited steps of the claimed methods are met by Bohm, and thus the claims are obvious in view of Bohm. Applicants traverse.

To the contrary of the assertion of the Examiner, how the program of Bohm functions is altered by input. The structure coordinates of the molecule or molecular complex indeed affect the manner in which the claimed process steps function or the way the computer containing the coordinates functions. The structure coordinates provide the parameters, metes and bounds within which the fitting operation is performed and therefore dictate the computer programs themselves. For example, the spatial relationship of the atoms established in the structure coordinates of the molecule or molecular complex determines the manner in which the docking program probes the surface of the molecule or molecular complex for shape complementarity or a particular energetically favorable, electrostatic or Van der Waals interaction in relation to the chemical entity. As a further example, the unique energy surface provided by the structure coordinates of the molecule or molecular complex dictates the cycle in which

the energy minimization algorithm search for local energy minima in pursuit of the global energy minimum. For example, the spatial relationship of the atoms set forth by the structure coordinates of the molecule or molecular complex determine how the molecular dynamics algorithm will integrate forces applied to the molecule or molecular complex and the chemical entity. Therefore, the structure coordinates of the molecule or molecular complex determine how the process steps of the claimed method are performed, and in so doing, alters how the computer upon which these calculations are performed functions.

Applicants direct the Examiner to the definition of "functional descriptive material" in MPEP 2106 IV B 1:

"Functional descriptive material consists of data structures and computer programs which impart **functionality** when encoded on a computer-readable medium. (The definition of "data structure" is "a physical or logical relationship among data elements, designed to support specific data manipulation functions." (emphasis added))"

There is indeed a spatial relationship between the structure coordinates of each atom in the molecule or molecular complex. This spatial relationship determines how the computer program for drug discovery and computer functions. Further, the structure coordinates of the molecule or molecular complex impart functionality by, for example, providing a quantified association between the chemical entity and the molecule or molecular complex to facilitate drug discovery, a utility recognized by the Examiner on page 2, lines 7-9 of the November 20, 2002 Office Action. The structure coordinates are not analogous to printed matter with no actual function, such as music or literary

works. Therefore, the structure coordinates of the molecule or molecular complex are functional descriptive material, and should be accorded patentable weight.

In addition, Bohm does not teach or suggest using the structure coordinates from IMPDH or a homologue thereof in combination with a process involving a fitting operation. Furthermore, as in claims 23, 29, 32, 38, 41 and 44, 47, 52, 55 and 58, and dependent claims, the starting material is a new and unobvious set of structure coordinates from IMPDH or homologue thereof, and the resulting materials are new, unobvious and unpredicted: a specific quantified association between the chemical entity and the IMPDH binding pocket or homologue thereof, an inhibitor specific for the molecule, molecular complex comprising the IMPDH binding pocket or homologue thereof, an assembled compound or complex that specifically associates with the IMPDH binding pocket or homologue thereof, and a set of chemical entities that associate with the binding pocket of IMPDH or homologue thereof of less than -7 kcal/mol. Therefore, claims 23, 27-62 are not obvious in view of Bohm. In view the above arguments, applicants request the withdrawal of the rejection under 35 U.S.C. §103.

CONCLUSION

Applicants respectfully request that the Examiner reconsider and withdraw all outstanding rejections, enter the proposed amendments and additions, and pass the resulting claims to allowance.

Respectfully submitted,

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Appendix of Amendments

We claim:

23. (Three times amended) A method for evaluating the ability of a chemical entity to associate with [a molecule or molecular complex comprising] a binding pocket of a molecule or molecular complex, wherein the binding pocket is defined by structure coordinates of all or part of Chinese hamster type II inosine monophosphate dehydrogenase ("IMPDH") amino acids 68, 69, 93, 273, 274, 275, 276, 277, 303, 322, 324, 325, 326, 327, 328, 330, 331, 332, 333, 334, 337, 339, 340, 364, 413, 414, 415, 416, 420, 439, 440, 441, 442, 469, and 470 according to Figure 1, or a homologue of said [molecule or molecular complex, wherein said homologue comprises a] binding pocket that has a root mean square deviation from the backbone atoms of said amino acids of not more than 1.5 Å, comprising the steps of:

a) employing computational means which utilize all or part of said structure coordinates and structure coordinates of a chemical entity, to perform a fitting operation [between] to associate the chemical entity [and a] with said binding pocket [of the molecule or molecular complex] or homologue thereof;

b) [analyzing the results of said fitting operation to] quantifying the association between the chemical entity and the binding pocket or homologue thereof; and

c) outputting said quantified association to a suitable output hardware.

27. (Amended) The method according to claim 23, wherein said binding pocket is defined by structure coordinates of IMPDH amino acids 275, 276, 303,

325, 326, 331, 333 and 441 [274, 275, 276, 277, 303, 322, 324, 325, 326, 331, 333, 414, 415, and 441] according to Figure 1, [or a homologue of said molecule or molecular complex, wherein said homologue comprises a] and the homologue of said binding pocket [that] has a root mean square deviation from the backbone atoms of said amino acids of not more than 1.5 Å.

28. (Amended) The method according to claim 27, wherein said binding pocket is defined by structure coordinates of IMPDH amino acids [275, 276, 303, 325, 326, 331, 333 and 441] 274, 275, 276, 277, 303, 322, 324, 325, 326, 331, 333, 414, 415, and 441 according to Figure 1, [or a homologue of said molecule or molecular complex, wherein said homologue comprises a] and the homologue of said binding pocket [that] has a root mean square deviation from the backbone atoms of said amino acids of not more than 1.5 Å.

29. (Amended) A method for evaluating the ability of a chemical entity to associate with a binding pocket of a molecule or molecular complex [comprising all or any parts of a binding pocket] defined by structure coordinates of all or part of IMPDH amino acids 67, 68, 69, 70, 73, 274, 275, 276, 303, 322, 323, 324, 325, 326, 327, 328, 329, 330, 331, 332, 333, 334, 335, 364, 365, 366, 367, 368, 385, 386, 387, 388, 389, 391, 411, 412, 413, 414, 415, 416, 419, 440, 441, 442, 443, 500, 501, 502, 503, 504, 505, and 506 according to Figure 1, or a homologue of said [molecule or molecular complex, wherein said homologue comprises a] binding pocket that has a root mean square deviation from the backbone atoms of said amino acids of not more than 1.5 Å, comprising the steps of:

a) employing computational means which utilize all or part of said structure coordinates and structure coordinates of a chemical entity, to perform a fitting operation [between] to associate the chemical entity [and a] with said binding pocket [of the molecule or molecular complex] or homologue thereof;

b) [analyzing the results of said fitting operation to] quantifying the association between the chemical entity and the binding pocket or homologue thereof; and

c) outputting said quantified association to a suitable output hardware.

30. (Amended) The method according to claim 29, wherein said binding pocket is defined by structure coordinates of IMPDH amino acids 68, 70, 322, 328, 329, 331, 332, 335, 364, 366, 387, 388, 411, 413, 414, 415, 441, 442, 501, and 502 [68, 69, 70, 303, 322, 326, 327, 328, 329, 330, 331, 332, 333, 335, 364, 365, 366, 367, 385, 386, 387, 388, 411, 413, 414, 415, 416, 419, 441, 442, 443, 501, 502, 503, and 504] according to Figure 1, [or a homologue of said molecule or molecular complex, wherein said homologue comprises a] and the homologue of said binding pocket [that] has a root mean square deviation from the backbone atoms of said amino acids of not more than 1.5 Å.

31. (Amended) The method according to claim 30, wherein said binding pocket is defined by structure coordinates of IMPDH amino acids [68, 70, 322, 328, 329, 331, 332, 335, 364, 366, 387, 388, 411, 413, 414, 415, 441, 442, 501, and 502] 68, 69, 70, 303, 322, 326, 327, 328, 329, 330, 331, 332, 333, 335, 364, 365, 366, 367,

385, 386, 387, 388, 411, 413, 414, 415, 416, 419, 441, 442, 443, 501, 502, 503, and 504 according to Figure 1, [or a homologue of said molecule or molecular complex, wherein said homologue comprises a] and the homologue of said binding pocket [that] has a root mean square deviation from the backbone atoms of said amino acids of not more than 1.5 Å.

32. (Amended) [The] A method [according to claim 29,] for evaluating the ability of a chemical entity to associate with a binding pocket of a molecule or molecular complex, wherein said binding pocket is defined by structure coordinates of all or part of Chinese hamster type II IMPDH amino acids 67, 68, 69, 70, 73, 93, 273, 274, 275, 276, 277, 303, 322, 323, 324, 325, 326, 327, 328, 329, 330, 331, 332, 333, 334, 335, 337, 339, 340, 364, 365, 366, 367, 368, 385, 386, 387, 388, 389, 391, 411, 412, 413, 414, 415, 416, 419, 420, 439, 440, 441, 442, 443, 469, 470, 500, 501, 502, 503, 504, 505, and 506 according to Figure 1, or a homologue of said [molecule or molecular complex, wherein said homologue comprises a] binding pocket that has a root mean square deviation from the backbone atoms of said amino acids of not more than 1.5 Å, comprising the steps of:

a) using a computer comprising a computer program for computational methods of drug discovery which utilize all or part of said structure coordinates and structure coordinates of a chemical entity to perform a fitting operation to associate the chemical entity with said binding pocket or homologue thereof;

b) quantifying the association between the chemical entity and the binding pocket or homologue thereof; and

c) outputting said quantified association to a suitable output hardware.

33. (Amended) The method according to claim 32, wherein said binding pocket is defined by structure coordinates of IMPDH amino acids [68, 69, 70, 274, 275, 276, 277, 303, 322, 324, 325, 326, 327, 328, 329, 330, 331, 332, 333, 335, 364, 365, 366, 367, 385, 386, 387, 388, 411, 413, 414, 415, 416, 441, 442, 443, 501, 502, 503 and 504] 68, 70, 275, 276, 303, 322, 325, 326, 328, 329, 331, 332, 333, 335, 364, 366, 387, 388, 411, 413, 414, 415, 441, 442, 501, and 502 according to Figure 1, [or a homologue of said molecule or molecular complex, wherein said homologue comprises a] and the homologue of said binding pocket [that] has a root mean square deviation from the backbone atoms of said amino acids of not more than 1.5 Å.

34. (Amended) The method according to claim [33] 32, wherein said binding pocket is defined by structure coordinates of IMPDH amino acids [68, 70, 275, 276, 303, 322, 325, 326, 328, 329, 331, 332, 333, 335, 364, 366, 387, 388, 411, 413, 414, 415, 441, 442, 501 and 502] 68, 69, 70, 274, 275, 276, 277, 303, 322, 324, 325, 326, 327, 328, 329, 330, 331, 332, 333, 335, 364, 365, 366, 367, 385, 386, 387, 388, 411, 413, 414, 415, 416, 441, 442, 443, 501, 502, 503, and 504 according to Figure 1, [or a homologue of said molecule or molecular complex, wherein said homologue comprises a] and the homologue of said binding pocket [that] has a root mean square deviation from the backbone atoms of said amino acids of not more than 1.5 Å.

35. (Amended) The method according to claim 32, wherein said molecule [or molecular complex] is defined by the set of structure coordinates of IMPDH amino acids according to Figure 1, and said molecular complex is defined by the set of structure coordinates of IMPDH amino acids and one or more of oxidized inosine monophosphate thioimidate intermediate (XMP*) and mycophenolic acid (MPA) according to Figure 1, or a homologue thereof, wherein said homologue has a root mean square deviation from the [conserved] backbone atoms of said IMPDH amino acids of not more than 1.5 Å.

36. (Amended) The method according to claim 32, wherein said molecule [or molecular complex]comprises amino acids 1-514 of IMPDH and said molecular complex comprises amino acids 1-514 of IMPDH, and one or more of, oxidized inosine monophosphate thioimidate intermediate ("XMP*"), and mycophenolic acid ("MPA").